UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,432	10/03/2006	Gregory D. Plowman	05-959-A5 (EX03-078C-US)	4479

20306 7590 02/01/2011

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
02/01/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,432	PLOWMAN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/15/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,15,16,18,20-22,24,25,31,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31* is/are allowed.

6)☒ Claim(s) *1-7,15,16,18,20-22,24,25,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4, 5, 15, 24 and 25 have been amended. Claims 1-7, 15, 16, 18, 20-22, 24, 25, 31, 34 and 35 are pending and under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 16, 22, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is vague and indefinite because it is unclear if recitation of "the assay" is in reference to the first assay system or the second assay system of claim 1.

Claims 15, 16, 24 and 25 are vague and indefinite because it is unclear if the "assay system" is in reference to the assay system of part (a) or part (d) of claim 35.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 15, 18, 20-22, 24, 25, 34 and 35 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a second assay system which is a cultured cell assay system or a transgenic mouse comprising the RIP-1-Tag2 transgene, does not reasonably provide enablement for a second assay system which is a non-human animal expressing MAP2K6 or a transgenic mouse expressing MAP2K6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A)As drawn to a transgenic mouse

Claims 15 and 224 embody a transgenic mouse tumor assay. The instant specification contemplates non-human animals which are genetically modified with respect to MAP2K6. The specification fails to teach how to make a transgene construct for the expression of MAP2K6 or provide objective evidence that the transgenic mouse expressing MAP2K6 had been made. Thus, the state of the art at the time of filing must be relied upon for the directives regarding the making of a transgenic mouse expressing MAP2K6. The MPEP classifies the physiological arts in general as unpredictable (section 2164.03). Logan and Sharma (Clin Exp Pharmacol Physiol, 1999, vol. 26, pp. 1020-1025) teach that the challenge for the development of a transgenic animal is in the appropriate design of a construct that allows for the expression of the gene of interest in the desired cell type at an appropriate level. In the instant case, the specification provides no guidance as to the target tissue for the expression of the MAP2K6 gene in the transgenic mouse, nor is guidance given regarding the type of promoters or enhancers useful for regulating the gene at the appropriate level in the transgenic mouse.

(B) As drawn to a transgenic animal expressing MAP2K6

Claims 1, 34 and 35 recite the embodiment of a "non-human animal expressing MAP2K6. When given the broadest reasonable interpretation, a "non-human animal" encompasses pigs, rabbits, goats, etc. It is recognized in the art, that the technology developed to generate transgenic mice is becoming predictable and reliable given an appropriate transgene construct , but that the application of this technology and construct to other animals is difficult and unreliable. The abstract of Charreau et al (Transgene Research, 1996, Vol. 5, pp. 223-234, cited in the previous Office action) teaches that although the procedure of microinjection into fertilized rat ova is an established procedure, transgenic rats remain difficult to produce in comparison with mice, and that fewer than 20 transgenic rat lines have become established by

1996. The abstract of Nancarrow et al (Methods in molecular biology, 1993, vol. 18, pp. 273-303, cited in a previous Office action) acknowledges that the production of transgenic sheep has proved to be very difficult compared to the production of transgenic mice. The abstract of Machaty et al (Cloning Stem Cells, 202, Vol. 4, pp. 21-27, cited in a previous Office action) states that although genetic manipulation of mice has been possible for over two decades, the technology of nuclear transfer and homologous recombination has not been effective for the production of transgenic pigs.

The specification does not teach the particulars of making a transgene construct wherein introduction of said transgene construct into mouse or a non-human animal produces a transgenic mouse or non-human animal, thus, the teachings of the art at the time the specification was filed must be relied upon for enablement. For the reasons set forth above, the art acknowledges that the application of the technology of making transgenic mice to the making of other non-human mammals is unreliable and unsuccessful, one of skill in the art would be subject to undue experimentation in order to make the broadly claimed transgenic animals and use them in the claimed methods.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704, cited in a previous action) in view of Engleman et al (Journal of Biological Chemistry, 1999, Vol. 274, pp. 35630-35638).

Stein et al teach a method for identifying a composition which affects MEK6 activity comprising incubating said composition and MEK6 kinase or a polynucleotide encoding said kinase for a time sufficient to allow the components to interact ad measuring the effect of the composition of MEK6 kinase or the polynucleotide encoding the kinase, under conditions whereby but for the presence of the test agent, the system provides a reference activity and (c) detecting a test-agent biased activity of the assay system (claim 24, figures 4, 5 and 7a, column 12, lines 16-18). Stein et al teach that test agent may include antibodies which neutralize MEK6, a competing peptide that represents the substrate binding domain of MEK6 or the dual phosphorylation motif of the MEK6 substrate, an antisense polynucleotide or ribozyme that interferes with the transcription or translation of MEK6, or a molecule that prevents transfer of phosphate groups from MEK6 to a substrate (page 7, lines 29-35). Stein et al teach that ansiomycin treatment or exposure to UV light was able to activate MEK6 (page 24, lines 6-11) which fulfills the specific embodiment of "modulate". Stein et al teach a second assay system comprising a coupled in vitro kinase assay to measure the activity of p38 in response to MEK6 (page 11, line 18 to page 12, line 36). Stein et al teach that antibodies and other agent having a desired effect on MEK6 activity may be administered to a patient to treat an existing disease in vivo, and that an agent which decreases MEK6 activity in vivo may be administered to treat inflammation, autoimmune diseases, cancer or degenerative diseases (page 17, lines 27-31)

Engleman et al teach that MKK6 activated p38 in vivo (page 35631, first column, lines 2-3 and page 35632, first column, first paragraph under the heading "MKK3/6 Activity Decreases over the Course of Adipocytes Differentiation") Engleman et al teach that activated MKK6 in the form of a MKK6 constitutively active mutant can spontaneously induce adipogenesis in 3T3-L1 cells by-passing the normal hormonal requirement (page 35634 under the heading "p38 Hyperactivation Leads to Spontaneous Adipogenesis in 3T3-L1 Cells"). Engleman et al teach that constitutively activated MKK6 in combination with a hormonal mixture can cause NIH-3T3 cells to differentiate into adipocytes (page 35636, under the heading of "MKK6(Glu) Can Induce Adipogenesis in NIH-3T3 Cells"). Engleman et al teach that salicylic acid mimics the effect of

the constitutively activated MKK6 by measurement phosphorylated p38 (Figure 5A). Engleman et al teach that variation between p38 activity may be one of the distinguishing features between the difference in adipogenic potential of NIH-3T3 cells and 3T3-L1 fibroblasts (pages 35637-35638, bridging sentence).

It would have been prima facie obvious at the time that the invention was made to substitute non-transfected NIH-3T3 cells and 3T3-L1 cells in the method of Stein et al and to screen both cell lines for activation of MKK6 in response to salicylates, and to screen both cell lines for additional small molecule drugs which can cause differentiation to adipocytes using both NIH-3T3 cells and 3T3-L1 cells and to measure the activation of MKK6 in response to said agents. One of skill in the art would have been motivated to do so by the teaching of Engleman who propose that the difference in p38 level between the two cell lines is responsible for the difference of adipogenic potential. Knowing the relationship between MKK6 and p38, one of skill in the art would want to assess the phosphorylation of endogenous MKK6 in addition to p38 in said cell lines.

Claims 1, 2, 15 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al (WO 02/05792) in view of Lackley et al (U.S. 5,342,947).

Simon et al teach the use of inhibitors of mitogen activated kinase kinase 6 useful for the treatment of cancer by inhibition of the down stream expression of matrix metalloproteases (abstract, page 5, lines 4-14). Simon et al suggests that the invasiveness of cancer cells can be modulated by administration of an active agent that inhibits regulators of the MMP-9 signal transduction pathway. Simon et al teach that MMK-6 is a regulator of the MMP-9 signal transduction pathway (page 22, lines 12-23 and page 23, lines 13-16) which includes p38. Simon et al teach different cell lines plated out on matrigel for a measurement of in vitro invasion of cancer cells (page 14, line 19 to page 16, line 2). Simon et al teach that an active agent of the invention is preferably a small molecule of low molecular weight such as MW<1000 (page 5, lines 16-22)/ Simon et al teach the p38 inhibitors of SB 203580 and SB 202190, which are known inhibitors of p38. Simon et al do not specifically describe specific inhibitors of MKK6, or a second assay system including a xenograft assay.

Lackely et al teach that human tumor xenografts heterotransplanted into nude mice are widely used to assess the anti tumor activities of a cancer chemotherapeutic agent (column 13, lines 29-34).

It would have been prima facie obvious to one of skill in the art at the time of filing to screen for small molecule inhibitors of MKK6, suggested by Simon et al to be potential agents useful in the inhibition of cancer invasion by using the Matrigel assay in conjunction with a xenotransplant assay. One of skill in the art would have been motivated to do so because Simon et al teach the Matrigel assay as indicative of tumor invasive capability and because Lackely et al teach that human tumor xenograft assay as replicating the drug sensitivity of human tumors in vivo.

Claim 31 is allowed.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. the abstract of Rindl et al (American Journal of Pathology, 1991, Vol. 138, pp. 1321-1334) which demonstates that the Rip-1Tag2 mouse was known in the art at the time of filing.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571)272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643